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Meta-analysis of three case controlled studies and an ecological study into the link between cryptogenic epilepsy and chronic toxoplasmosis infection

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Ecological study

Summary A meta-analysis was performed on three case controlled studies which examined the relationship between latent toxoplasmosis gondii infection in the immunocompetent host and cryptogenic epilepsy. Further comparison was also made by examining the seroprevalence of toxoplasmosis rates for 17 various countries, cities or regions against the prevalence rates for epilepsy in those regions.
Results: The results for the meta-analysis showed a log-odds ratio of 4.8 which approximates to a similar relative risk, (CI 2.6 to 7.8), with CI for all three studies being above 1. Seroprevalence rates for toxoplasmosis and prevalence rates of epilepsy showed a strong association ($p < 0.001$).
Discussion: The prevalence of toxoplasmosis is an important factor in the prevalence of epilepsy with a probable link in the cryptogenic epilepsies. An area with a reduced burden of toxoplasmosis will also have a reduced burden of epilepsy. Neuropathophysiology findings from various studies show a common physical relationship of microglial nodule formation in *Toxoplasma gondii* infection and epilepsy. This analysis raises the possibility that one of the many causes of epilepsy may be an infectious agent, or that cryptogenic epilepsy may be a consequence of latent toxoplasmosis infection. This raises the possibility that public health measures to reduce toxoplasmosis infection may also result in a reduction in epilepsy.

Introduction

Epilepsy, like anaemia is a sign with many causes, with 1% of the general population being affected.[1] However, about 20% of epileptic patients have an

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epilepsy of unknown cause[2] (cryptogenic epilepsy). The short-term consequences of toxoplasmosis are well known—a short flu like illness, with no reported long-term consequences. In chronic toxoplasmosis infection the organism can live in any of the body tissues, with a predisposition for the brain and muscle[3] and remains alive for the whole life of the individual with no apparent ill effects.

Immunocompromised individuals are at risk of reactivating a latent toxoplasmosis infection. In the brain, toxoplasma encephalitis can develop or, if situated in any other tissues abscesses may form.[4,5] This paper endeavours to determine if *Toxoplasma gondii* may be associated with epilepsy.

Method

For the meta-analysis a database search for case—control studies of toxoplasmosis and epilepsy, using the Cochrane database and Medline: search terms were: [toxoplasmosis or *Toxoplasma gondii*] and [epilepsy or cryptogenic, epidemiology of epilepsy] were conducted. The complete yield of results was only three case—controlled studies, none of the three were excluded from this meta-analysis.

The data were analysed using STATA statistical software; the odds ratios from each study were combined using a random-effects model.

An ecological study was also conducted. Studies documenting the prevalence of epilepsy in specified countries were sought. (Search terms used were: epidemiology of epilepsy, prevalence, population based study) Separately studies documenting the prevalence of toxoplasmosis in specified countries were sought. (Search terms used were: epidemiology of toxoplasmosis, seroprevalence, prevalence, *Toxoplasma gondii*, pregnant) and all countries for which an estimate of the prevalence of both epilepsy and toxoplasmosis were identified. Necessarily the overall prevalence of epilepsy was documented rather than the prevalence of cryptogenic epilepsy or other subgroups because such data were infrequently documented.

Seroprevalence of toxoplasmosis was reported either in pregnant women in a country or region (Fig. 2) or seroprevalence throughout a general population (Fig. 3). The prevalence of both toxoplasmosis and epilepsy have been falling over the last few decades[6—8] so countries or regions were included only if the time difference between the estimates of toxoplasmosis and epilepsy was less than 20 years.

A scatter plot from the combined data obtained in Figs. 2 and 3 has also been performed (Fig. 4).

Studies were searched for on the Cochrane database as well as the 'Medline' site, which is a division of U.S. National Library of Medicine, using the search terms stated above.

Results

Three case-control studies were identified and included in the meta-analysis shown in Fig. 1.[9—11] In the meta-analysis itself the size of the squares are proportional to the size of the study. The prevalence of toxoplasmosis in epileptics and controls in each study are shown in Table 1. The summary odds ratio (approximating a relative risk) from the three studies is 4.8 (95% confidence interval (2.6 to 7.8)), indicating that epilepsy is 4.8 times more prevalent among persons seropositive for toxoplasmosis than the seronegative ones. There was no heterogeneity between the studies.

The ecological study showed a strong association between the prevalence of epilepsy in countries, cities or regions and the seroprevalence of toxoplasmosis both in pregnant women (Fig. 2) and

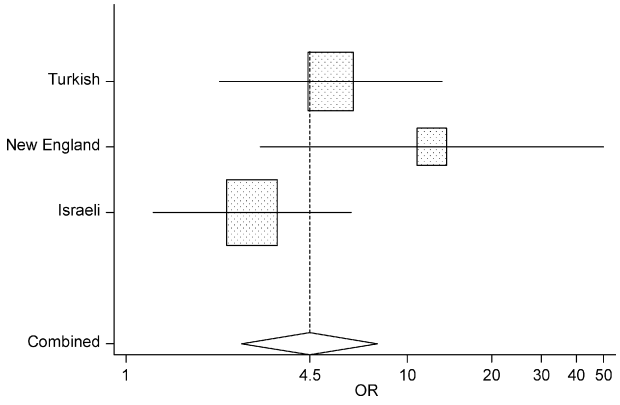

Figure 1 Log-odds ratio forest plot for the three above studies. Turkish study the log-odds ratio is 5.3 (CI 2.1—13.3), New England study the log-odds ratio is 12.2 (CI 3.0—49.9), Israeli study the log-odds ratio is 2.8 (CI 1.2—6.3). Combined log-odds ratio is 4.8 (CI 2.6—7.8). There was no heterogeneity between studies.

Table 1 Occurrence of toxoplasmosis in epileptic patients in the three studies under analysis

Outcome	Study group	Control group	Total
Turkish Study[7], pub 2003, *p*-value <0.01			
Toxo +ve	27	9	36
Toxo −ve	23	41	64
Total	50	50	100
New England Study[8,a], pub 2001, *p*-value 0.013			
Toxo +ve	17	5	22
Toxo −ve	5	18	23
Total	22	23	45
Israeli Study[9], pub 1995, *p*-value 0.11 (0.03 for any neurological disorder)			
Toxo +ve	21	10	31
Toxo −ve	74	99	173
Total	95	109	204

*Using figures for the study as a whole, which included epilepsy, cerebral palsy and nerve deafness and their relationship with toxoplasmosis. In the Israeli study they were studying cerebral palsy, epilepsy and nerve deafness, the exact number in each group was unknown but a third of the total group was implied, 32 is an underestimated figure.

[a] For the control group, the paper stated a background rate of 20% for seroprevalence of toxoplasmosis. It was unclear if this was the figure the paper had obtained which is also the standard background prevalence in this part of the U.S.A.

the general population (Fig. 3) within the same region. The scatter plot (Fig. 4) shows a strong association ($p < 0.001$) between the seroprevalence of toxoplasmosis and the prevalence of epilepsy, both in pregnant women ($r = 0.98$) and in the general population ($r = 0.91$).

Discussion

The meta-analysis shows that epilepsy especially cryptogenic epilepsy, may to some degree, be associated with toxoplasmosis. The ecological study and the scatter plot both show an association. A regression line has not been placed on the scatter plot as the association may appear exaggerated and may be due to confounding.

In Figs. 2 and 3 a trend is seen, in that the higher the seroprevalence of toxoplasmosis, the higher the rate of epilepsy in the population. It should be noted that in the majority of the above studies (Figs. 2 and 3) there was increased seroprevalence of toxoplasmosis antibodies with advancing age, low economic status and low educational background. While some

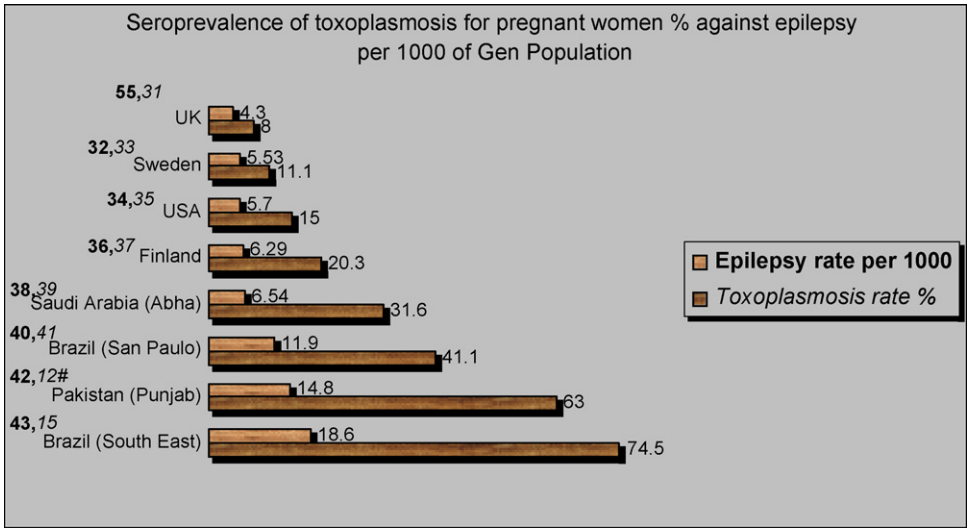

Figure 2 Graph comparing seroprevalence of toxoplasmosis for pregnant women (percentage of population) against epilepsy per 1000 of general population, by country. Words in brackets are regions or areas from which data was compared. References given are bold for epilepsy and italics for toxoplasmosis.[#]This toxoplasmosis rate is high in this area. In the remainder of Pakistan the rates that have been reported are much lower.

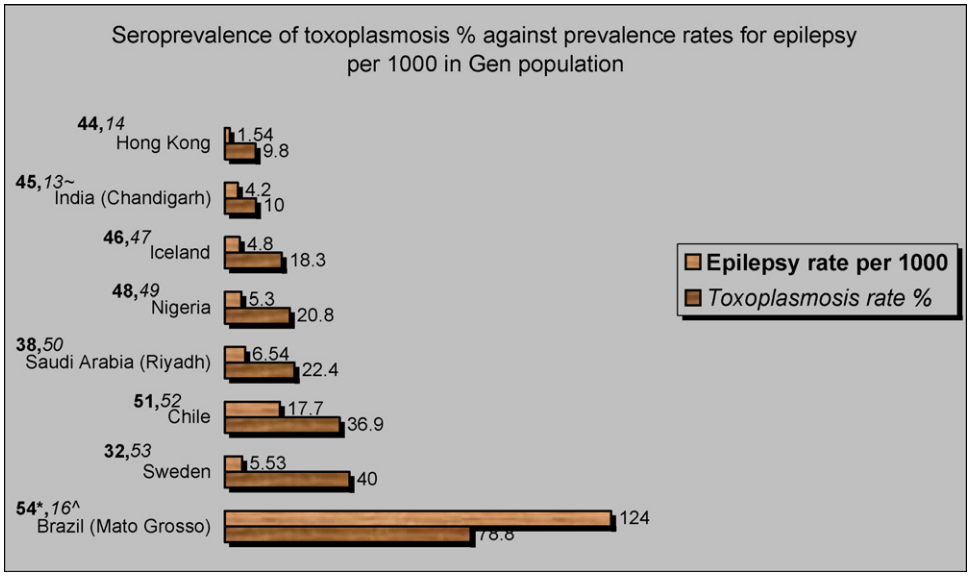

Figure 3 Graph comparing seroprevalence of toxoplasmosis in general population (percentage of population) against epilepsy per 1000 of general population, by country. Words in brackets are regions or areas from which data was compared. References given are bold for epilepsy and italics for toxoplasmosis.^Seroprevalence of toxoplasmosis in Enawene-Nawe tribe in the Brazilian state of Mato Grosso.*Epilepsy rate for active epilepsy was reported as 12.4%, inactive was 6.2% and a total prevalence given as 18.6% for the Bakairi Indians, in the Brazilian state of Mato Grosso.~Prevalence in population were given as 5.4% were positive for IgM and 4.66% showed IgG antitoxoplasma antibodies. Thus, a total prevalence is stated as 10 in this report.

studies showed a higher rate in rural areas compared to urban areas, many did not.[10,12–14] This was usually due to other factors regarding cat ownership, contact with soil, age, social status and economic differences in the populations being studied or cultural differences.[10,14–17]

As can be seen from Fig. 3, the Brazilian statistics, while holding true to observed relationship of 'high toxoplasmosis rate, high epilepsy rate', the epilepsy rate seems disproportionately large. There are various possible reasons for this; the most logical is that there are many causes of epilepsy, toxoplasmosis being one cause. Also the poorer a region, the higher the morbidity afflicting that region, this relationship is demonstrated in Fig. 2, where the lowest rates for epilepsy and toxoplasmosis come from wealthy countries and the highest come from less well off or countries with poorer living standards for the general population.

Whether toxoplasmosis is a confounding factor in epilepsy should be relatively easy to disprove. It should be possible to find a country, area or city

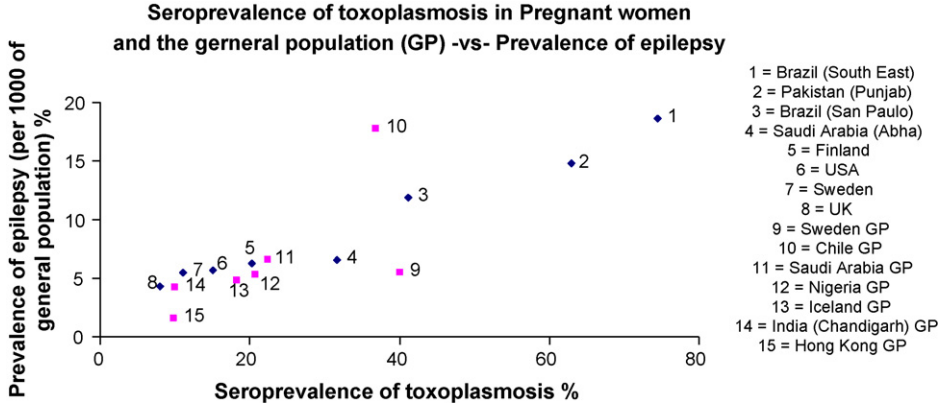

Figure 4 Scatter plot combining the data from Fig. 2 and 3 showing the seroprevalence of toxoplasmosis for pregnant women (diamonds) and the general population (squares) against prevalence of epilepsy. The data point for Brazil Mato Grosso has been excluded from the scatter plot as it is an outlier and skews the remaining data. The correlation coefficients show a strong association ($p < 0.001$) between the seroprevalence of toxoplasmosis and the prevalence of epilepsy, both in pregnant women ($r = 0.98$) and in the general population ($r = 0.905$).

where the toxoplasmosis rate is low while the rate of epilepsy is very high or vice versa. Although this is an easy task to perform for other diseases that are suspected of causing some forms of epilepsy, for example CMV. The CMV rate in Hong Kong is over 80% compared to the low rate of epilepsy, which is 1.54 per 1000. This is not so for toxoplasmosis, indeed no country, city or region which goes against this trend could be found, unless like with like was not compared. Some regions in India or Pakistan show a high epilepsy rate while other regions show a low toxoplasmosis rate, but when a same/similar region or a similar ethnic group is compared within a region the relationship of high toxoplasmosis rate and high epileptic rate still appears to holds true.

The above trend is also confirmed by the gradual decline over the decades seen in the incidence of cryptogenic epilepsy[11] and toxoplasmosis.[3,10] The prevalence of epilepsy is falling over time, as is toxoplasmosis, the fall in the rate of toxoplasmosis is due to increased personal and food hygiene, and the precautions taken in the preparation of red meats. For pregnant ladies, the advice of not eating undercooked meat and taking care when changing the cat litter tray have all had an effect on the reduction of the toxoplasmosis rate. Although there are vaccine candidates for toxoplasmosis gondii,[18] none have been proven and as toxoplasmosis gondii belongs to the same phylum (Apicomplexa) as malaria, such a vaccine maybe exceptionally difficult to obtain.

Proposed pathophysiology of how *Toxoplasma gondii* could cause epilepsy

The tissue cyst distribution of *Toxoplasma gondii* is dependent on the immunocompetency of the host, epigenetics of the host and the strain of *T. gondii*. In animal models it is proposed that some tissue cysts rupture and in doing so causes marked inflammation of that area and hence triggers microglial formation which may represent the 'tombstones' of Toxoplams cysts[18] and lead to scar tissue formation. It has also been demonstrated that the formation of new generation of tissue cysts is possible in chronically infected mice, but the mechanism of exit and entry into a cell, is as yet not fully understood.[19] Microglial nodules have also been found in some viral diseases,[20–22] and have been described in patients with glioneuronal tumors.[23] This may account for the finding that not all cryptogenic epileptics test positive for *Toxoplasma gondii*. However, when comparing the prevalence rates of epilepsy with those of CMV seroprevalence, there was no correlation.

In epilepsy the formation of scar tissue has been suggested to be one of the main theories for the cause of epilepsy and has been supported by many studies.

Scar tissue in the brain can be present due to many kinds of pathology initially microglial are prominent after the initial insult. After a period of time, a dense fibrous gliosis is laid down; how microglia are related to the formation of scar tissue is unknown, but seem to be related, the microglia being the first step in this pathology[24,25]. It should be noted that the incidence or prevalence of microglial nodules in the general population could not be found.

Another possible initiation event for an epileptic seizure is when *T. gondii* has entered the cell, it is then able to hijack the host cell Ca^{2+} pump. When *T. gondii* exits the host cell there is a rise in $[Ca^{2+}]$ in the host which allows *T. gondii* to escape and subsequent lysis of the host cell occurs[26]. This lysis will also cause microglial formation[18].

Epileptic discharge may occur with a membrane defect leading to instability of the resting potential and/or abnormalities of potassium conductance, calcium channels, GABA inhibitory system[27]. In animal models, ablation of Ca channels does demonstrate seizure resistance[28] and differing membrane permeability to Ca^{2+} does lead to a change in the firing threshold of the affected neurone[29]. Whether Toxoplasma's ability to change the $[Ca^{2+}]$ within the cell of which it resides could be a pathway to induce an epileptic seizure is unknown but remains a possibility.

Conclusion

The evidence presented in this study seems to indicate that toxoplasmosis is a disease of age, social and economic poverty. The risks of which are reduced with increased economic prosperity and health provision.

The prevalence of toxoplasmosis is an associated factor in the prevalence of over-all epilepsy with a more probable link in the cryptogenic epilepsies. An area with a reduced burden of toxoplasmosis will also appear to have a reduced burden of epilepsy.

The neuropathophysiology findings from various studies[18,25,30] show that there is a physical relationship of microglial nodule formation in *Toxoplasma gondii* infection and in epilepsy. Whether this provides data to support the concept that one of the many causes of epilepsy may be an infectious agent or that cryptogenic epilepsy is a consequence of latent toxoplasmosis infection may only be confirmed with a more directed study.

There is clearly an association between toxoplasmosis and epilepsy and an association is plausible,

but this association may be exaggerated by confounding in the data (that is, people with toxoplasmosis may be more likely to have other causes of epilepsy). Other work that could be performed to take this theory forward could be larger case controlled study.

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